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ABSTRACT

Patients and methods: This is a cross sectional study comparing the retinal features of optic neuritis (ON) between 20 multiple sclerosis (MS) and 16 neuromyelitis optica (NMO) patients with a history of ON (visual acuity at time of attack ≥20/100) matched for age and gender using optical coherence tomography (OCT) and fundoscopy.

Results: Compared with MS, NMO patients often had: (1) vascular changes, including attenuation of the peripapillary vascular tree (3/40 MS eyes, 22/32 NMO eyes; p = 0.001) and focal arteriolar narrowing (0/40 MS eyes and 9/32 NMO eyes; p<0.0001), (2) a lower average nerve fibre layer (NFL) thickness (59.2 μm compared with 82.0 μm in MS; p = 0.004) and (3) nearly twice the NFL thinning after controlling for final visual acuity (32.1 vs 17.6 μm; p = 0.004). Patients with NMO had more severe and diffuse axonal injury of the NFL compared with MS.

Conclusion: These NFL and fundoscopic findings suggest that some of the injury seen in NMO may be vascularly mediated. These inner retinal vascular changes are reminiscent of blood vessel wall thickening previously reported in the optic nerve and spinal cord at autopsy. If the retinal changes share a common pathology to those in the spinal cord and optic nerve, these observations suggest that vascular changes may be detectable during life.

Neuromyelitis optica (NMO) is a CNS demyelinating disease characterised by relatively selective injury to the optic nerve and spinal cord. Given its generally recurrent and aggressive course, distinguishing NMO from multiple sclerosis (MS) in patients presenting with optic neuritis (ON) is important. Previous reports have not described clear ophthalmic differences between ON in NMO and MS.

We present evidence that NMO ON includes distinct vascular and retinal nerve fibre layer (NFL) changes on ophthalmoscopy and optical coherence tomography (OCT). These findings may be diagnostically useful and could have implications for understanding NMO pathogenesis.

METHODS

This was a cross sectional study of 16 NMO and 20 MS patients selected for persistent visual deficits after ON who were matched for: prior ON history (visual acuity nadir of at least 20/100), gender and age. NMO and MS patients with known ophthalmological disease (eg, glaucoma, cataract) and ON within the previous 3 months were excluded. This study received institutional review board approval and written informed consent was obtained from each subject in accordance with the Declaration of Helsinki.

The mean age of the NMO and MS subjects was 41 (11.7) years. Disease duration for MS and NMO subjects was 5.0 and 5.5 years, respectively. A total of 80% of MS subjects and 87% of NMO subjects were women; 75% of MS and 44% of NMO subjects were white; and 69% of NMO subjects were seropositive for anti-aquaporin 4 (AQP4) antibodies. ON occurred in 24 MS and 27 NMO eyes (p = 0.028). The final visual acuity (logMAR) of ON affected MS eyes was 0.44 (−20/60), range 0–2) and 0.81 (−20/120, range 0–3) for NMO eyes (p = 0.056).

Best recorded monocular visual acuity, with correction when appropriate, was used for all analyses. Each patient underwent a dilated fundoscopic examination with retinal photographs. The Fast Retinal Nerve Fibre Layer thickness protocol was performed on a Stratus OCT machine (Zeiss, Fremont, California, USA) by a trained technician masked to the patient’s diagnosis. Scans were repeated twice and assessed for signal strength and centring. Signal strength scores of 6 or less were not used. Two NMO patients were unable to undergo OCT because of inability to support weight while seated upright.

Optic disc pallor was assessed (absent, sectoral or global) and graded (mild, moderate and severe). Retinal photographs documented retinal vascular appearance in the peripapillary and midperiphery retina and were evaluated using modified Atherosclerosis Risk in Communities criteria. Vascular changes were described as involving arteries, veins or both. Narrowing of all vessels arising from the disc was categorised as global, whereas narrowing of localised vessel or area of vessels leaving the optic disc was categorised as sectoral. Narrowing of the blood column in an arterial branch with obscuration of the vessel lumen was categorised as “frosting”. These changes were not described as “sheathing” in a retinal vessel wall with narrowing.” Retinal changes were confirmed by an examiner masked to the subject’s diagnosis (overall agreement between examiners was 88%, kappa = 0.81).

STATA 9.0 (North Fork, Texas, USA) was used for statistical analyses. Logistic analyses were adjusted for clustering by individual, gender, race (white versus non-white), age, history of ON and final visual outcome where appropriate.
RESULTS
We found that, relative to MS, ON in NMO was associated with: (1) vascular changes involving the arterial blood supply to the inner retina, (2) greater axonal loss and (3) broader topographic patterns of axonal injury.

Three overlapping patterns of arteriolar changes were observed in NMO patients. The most prominent and common pattern was attenuation of arterioles in the peripapillary retina often with accompanying venous (fig 1A). Narrowing of arterioles was severe enough in many cases to give the vessel wall a thickened appearance. Sometimes, the peripapillary vascular attenuation was sectoral and, in these cases, appeared more prominent in arterioles compared with veins (fig 1B), a pattern sometimes observed after ischaemic optic neuropathy. Collectively, these changes (fig 1A, 1B) were seen in 22 of 32 eyes from patients with NMO but in only three of 40 eyes of patients with MS (p = 0.001). These patterns occurred in MS only when severe papillitis accompanied ON. MS eyes more commonly showed classic segmental (frequently temporal) disc atrophy, with or without slits, in the arcuate bundles but with normal appearing vessels (fig 1C). Venous sheathing was not seen in the MS eyes.8 9 In MS cases with pronounced disc
atrophy, vascular changes were not observed suggesting that the vascular changes common in NMO were not dependent on the severity of ON (fig 1D).

A second less common pattern observed in NMO demonstrated more selective and focal arteriolar “frosting” in vessels at a distance greater than two disc diameters from the disc edge (fig 1E). This was seen in 9/32 NMO eyes and was never seen in MS eyes (p<0.0001). In a single case examined, leakage of fluorescein was not observed from these “frosted” vessels (fig 1F). An association between anti-AQP4 autoantibodies and retinal vascular changes was not found (p = 0.279) although the cohort size was too small to detect a modest correlation.

Despite adjusting for gender, age, race and final visual outcome, NFL thinning in NMO was more diffuse and severe than in MS (table 1). In MS, ON reduced the NFL thickness by 17.6 μm and by 32.1 μm in NMO. As previously reported,10–11 NFL thinning in MS ON was predominantly temporal (fig 1G). In contrast, NFL thinning in NMO involved all quadrants and sometimes preserved axons mediating central vision (fig 1H and supplementary fig 1 available online).

Although NFL thinning is generally more severe in NMO, the extent of thinning in the temporal quadrant (which corresponds to the fibres forming the maculopapillar bundle) is equivalent in NMO and MS (see supplementary fig 1C online). Therefore, the average lower total NFL thickness scores in NMO appear to be related to more profound injury in arcuate and nasal fibres than in MS.

**DISCUSSION**

We reported previously unrecognised ophthalmological features that help distinguish ON of NMO from MS including: (1) attenuation of the peripapillary vascular tree, (2) focal arteriolar narrowing sometimes associated with obscuration of the vessel lumen, (3) approximately twofold thinning of the NFL and (4) diffuse thinning of the NFL rather than concentrated maculopapillar bundle thinning. These findings could serve as predictors of disease state following severe ON (visual acuity <20/100). Moreover, the vascular changes seen on fundoscopy can be readily evaluated by a trained examiner and the inter-examiner correlation was excellent (overall agreement 88%, kappa = 0.81). Because both vascular changes and extent of retinal NFL thinning are correlated with NMO, the cross sectional nature of this study cannot resolve whether the reported vascular changes precede or occur independently from retinal NFL thinning. Prospective studies are needed to confirm and extend these observations.

The cause of the vascular changes described in NMO is unclear. Some component of the vascular attenuation may be secondary to reduced metabolic demand with inner retinal atrophy. However, MS cases with severe inner retinal atrophy and global disc pallor but normal vessel appearance— as evidenced in fig 1D (global RNFL = 55 μm)—argue against this explanation. Global attenuation of the vascular tree could also be caused by prior optic disc oedema and secondary vascular compromise. Indeed, anecdotes suggest that NMO ON is associated with optic disc oedema.12–13 Therefore, vascular injury may be partially mediated by mechanical factors at the optic nerve head. However, previous pathological series described abnormally thickened vessel walls with narrowing of the vessel lumen in the retrobulbar optic nerves and spinal cords of NMO patients.14–16 Vascular hyalinisation of the spinal cord pathologically distinguishes NMO from MS although the mechanism of hyalinisation is not understood.15

Several pathological reports commented on the presence of inflammatory cell infiltration into the vessel walls of the optic nerves/chiasm in NMO patients.14–17 Therefore, some of the arteriolar changes described here, particularly “frosting”, may result from direct vascular inflammation. It is possible that anti-AQP4 autoantibodies participate in this process. AQP4 is expressed on the abluminal surface of endothelial cells in unfenestrated capillaries from the CNS, as well as in the astrocytic end feet that supply the tight junction of the blood–brain barrier.17 AQP4 is known to upregulate in response to injury and is present in the walls of astrocyte associated18–20 and inner retinal arterioles.21

The observation that all four quadrants of the NFL are thinned in NMO confirms a recent report of global NFL layer thinning in NMO detected by OCT.22 The greater magnitude of average NFL thinning in our series is presumably because only eyes affected by ON were studied. The pattern of global NFL thinning may be causally related to the described vascular changes. Vascularly mediated optic neuropathies such as glaucoma and non-arteritic anterior ischemic optic neuropathy are known to cause injury to the arcuate fibres of the NFL.23–24 This is in contrast with MS associated ON where injury is relatively more selective for the maculopapillar bundles.10–11 Therefore, the pattern of global NFL thinning is more consistent with a vascular process. We speculate that vasculopathy may play a direct role in tissue injury in NMO. It seems plausible that directly addressing vascular compromise, or disc oedema, might be therapeutically beneficial in NMO.

In summary, we describe a distinct pattern of NFL and vascular injury in NMO compared with MS. Further clinical studies incorporating OCT and fundoscopy could help improve the accuracy and speed with which NMO is diagnosed following ON: a clinically important distinction given the high risk for devastating outcomes and the availability of potentially beneficial treatments.25–27

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**Table 1** Fundoscopic and optical coherence tomography differences between optic neuritis in neuromyelitis optica and multiple sclerosis

<table>
<thead>
<tr>
<th></th>
<th>NMO</th>
<th>MS</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar changes (n = eyes)</td>
<td>22/32</td>
<td>3/40</td>
<td>0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>Arteriolar frosting (n = eyes)</td>
<td>9/32</td>
<td>0/40</td>
<td>0.0024</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NFL thickness (μm) (mean (SD))</td>
<td>59.2 (16.2)</td>
<td>82.0 (17.6)</td>
<td>&lt;0.0001</td>
<td>0.004</td>
</tr>
<tr>
<td>M:T ratio (mean (SD))</td>
<td>2.67 (0.70)</td>
<td>3.38 (0.78)</td>
<td>0.011</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Two sided Fisher’s exact p values are reported for the unadjusted analyses. Adjusted analyses used multivariable models adjusting for race, final visual acuity, sex and age. Average values are only reported for eyes with a history of optic neuritis. All analyses include clustering adjustment (two eyes from each patient).

MS, multiple sclerosis; M:T ratio, the ratio of the maximum NFL thickness in the arcuate bundles to the average temporal quadrant NFL thickness; NFL, mean nerve fibre thickness; NMO, neuromyelitis optica.
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Competing interests: None.

Ethics approval: Ethics committee approval was obtained from the University of California San Francisco.

REFERENCES